NOV 06 2001

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Received by

To:

PEDIGO, Paul F.
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street
Suite 4000
Charlotte, NC 28234-4009
ETATS-UNIS D'AMERIQUE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	29.10.2001
REPLY DUE	**within 1 month(s) and 15 days** from the above date of mailing

Applicant's or agent's file reference	International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
4848-37-1 204836	PCT/US00/41070	04/10/2000	04/10/1999

International Patent Classification (IPC) or both national classification and IPC

A61K47/48

Applicant

SHEARWATER POLYMERS, INC. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

Extension till Dec 26th requested JSY

- I ☒ Basis of the opinion
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04/02/2002.

Name and mailing address of the international preliminary examining authority:	Authorized officer / Examiner
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vogt, T Formalities officer (incl. extension of time limits) Velez, M.D. Telephone No. +49 89 2399 2615

Form PCT/IPEA/408 (cover sheet) (January 1994)

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):*

Description, pages:

1-23 as originally filed

Claims, No.:

1-29 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
   see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

   ☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4, 7-10, 13, 14 and 16 NO
Inventive step (IS)	Claims	1-29 NO
Industrial applicability (IA)	Claims	1-29 YES

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

II Priority (Art. 8 PCT).

The present application validly claims priority to the filing date of US-applications 60/166589 (19.11.1999) and 60/157503 (04.10.1999).

IV Lack of unity of invention (Rule 13 PCT).

The following independent claims are identified:

Claim 1: A conjugate between a peptide and a non-peptidic water soluble polymer, and

Claim 16: A composition comprising the conjugate of claim 1, and

Claim 17: A method for delivering the conjugate of claim 1 to the brain, and

Claim 27: A method for delivering an agent to the brain comprising administering a conjugate comprising the conjugate of claim 1 and the agent covalently bound to the polymer thereof.

The linking concept between the independent claims is the conjugate of claim 1. As explained under point V of this opinion this linking concept is not novel over D2. The independent claims are therefore not linked through a single novel and inventive concept and the present application so lacks unity of invention (Rule 13 PCT).

The following two inventions are therefore identified:

Invention A: A conjugate between a peptide and a non-peptidic water soluble polymer, A composition comprising the same, and a method for delivering the same to the brain (Claims 1-26), and

Invention B: A method for delivering an agent to the brain, comprising administering a conjugate comprising the conjugate of claim 1 and the agent covalently bound to the polymer thereof (Claim 27-29).

V Reasoned Statement (Rule 66(2) PCT).

Subject matter of the present application.

The provision of conjugates comprising a peptide and a water soluble non-peptidic polymer.

Cited prior art documents (Rule 64(1) PCT).

D1: WITT ET AL. (08.2001) J. PHARM. EXP. THERAPEUT., AM. SOC. PHARM. 298, 848-856.
D2: WO 95 00162 A
D3: WO 91 16929 A
D4: US-A-5 932 462
D5: US-A-5 681 811
D6: WO 00 78302 A
D7: WO 01 12230 A

D1 does not form part of prior art under Rule 64(1)or (3) PCT.

Whether the content of D6 and D7 is relevant for the assessment of the novelty and inventive step of the claimed subject matter of the present application will only be investigated in the European regional phase, and will essentially depend on the examination of the validity of the priority claims of D6 and D7, which at present is not possible.

Novelty (Art. 33(2) PCT).

D2 relates to conjugates of peptides with non-antigenic polymers (eg. PEG). D2 states that this modification results in a longer lifetime. The problem solved by D2 is to control the number and location of polymers attached to a peptide, to make sure that the bioactivity of these peptides is not hampered by steric hindrance of the covalently attached polymer (cf. p. 2). D2 solves this problem by making sure that the polymer can only attach to one of the termini of the peptide. Peptides suitable for the invention of D2 are: dynorphin A, neo-endorphins, and opioid peptides (p. 7, l. 28-30). In example 6 of D6, dynorphin A and two endorphin derivatives are conjugated to PEG-5K. D6 does not mention the BBB, but the transport across the BBB is considered to be an inherent property of the mentioned peptides (see also point VIII below).
Hence, D2 is prejudicial to the novelty of the subject matter of claims 1, 2, 4, 7-10, 13, 14 and 16.

D3 does not appear to contain information relevant to the present application.

D4 discloses multi-armed mono functional PEG for conjugation to proteins to increase the life span thereof. D4 mentions that thousands of proteins and enzymes can be

modified with the multi-armed mono functional PEG and mentions dynorphin in particular (col. 36, l. 42).
Hence, D4 is prejudicial to the novelty of the subject matter of claims 1, 2 and 8-10.

D5 discloses conjugates of bioactive agents with a non-peptidic polymer characterised in that the polymer comprises a hydrophilic and a lipophilic moiety. D5 anticipates endorphins, enkephalins (cf. claims 37-47).
Hence, D5 is prejudicial against the novelty of the subject matter of claims 1-3.

Inventive step (Art. 33(3) PCT).
D2 anticipates 'opioid peptides' for use in its invention. The peptides of claims 3, 5 and 6 all belong to this group, and are therefore anticipated by D2.

The optimum size of the polymer (claim 12) is considered to be a matter of standard laboratory experimentation, and is the result of two mechanisms: 1) life time (increases with increasing Mw), and 2) transport rate across the BBB (decreases with increasing Mw). Claim 12 therefore also lacks an inventive step.

Claims 17-26 are construed to read 'The conjugate of claim 1 for use as a medicament, the use of the conjugate of claim 1 for preparing a medicament'. These claims are only patentable with a patentable compound claim as the use of such conjugates appears to be inherently anticipated by D2.

The conjugate of claim 27 differs from the conjugate of claim 1 in that it comprises a bi-functional polymer. This subject matter appears not to be searched. Nevertheless, the subject matter does not appear to meet the requirement of inventive step over standard drug targeting strategies using conjugates of a ligand (eg. growth factors) and a bioactive compound (eg. marker, drug, etc.). The examiner knows from experience that these documents are available (see for instance WO-A-00/07543 for a recent publication).

Industrial applicability (Art. 33(4) PCT).
For the assessment of the present claims 17-29 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for

example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VII Defects in the description (Art. 5 PCT).

Although not stated in the application, one of the important features of the application is that the peptides must be modified at the N- or C- terminus. PEGylation of the peptides somewhere in the middle of the peptide (eg. via a Lys) would unavoidably lead to a decrease in transport and possibly even abolish transport as a whole, because the transport envisaged by the applicant is receptor mediated endocytosis.
This very important feature is not mentioned in the application, although the PEGylated peptides exemplified in the description are all N-terminal PEGylated. The application is therefore not considered to be enabling for those peptides having a reactive group in any other position then the C- or N- terminus (Art. 5 PCT). To overcome this objection the applicant should restrict the scope of claim 1 to those peptides that lack a reactive side chain in a position other then one of the termini, and are specifically disclosed in the description.

To meet the requirements of Rule 5 PCT the applicant is requested to identify D1

VIII Clarity of the claims (Art. 6 PCT).

The phrase 'wherein said peptide is stabilized in circulation' (claim 1) is written as a result to be achieved. It is assumed that this result is achieved by the water-soluble non-peptidic polymer.

Claim 1 further states that the conjugate should pass through the BBB of a mammal. Since this requirement cannot be the result of the conjugation, the applicant should indicate, which features lead to this result. From the description it is deduced that this feature is determined by the peptide **alone** (see also point VII), through receptor mediated processes.

In claim 6 the applicant refers to the peptide DPDPE. The applicant should write the

name of this peptide in full.

The term 'non-transportable agent' is unclear and appears to be a contradiction in terms, because the non-transportable agent is transported by the conjugate and is thus, transportable.

In claims 17 and 27 the applicant uses the phrase 'transporting the conjugate across ...' to indicate that the conjugate has to pass the BBB, as part of the method. The term 'transporting' implies an additional action by the applicant. However, the peptides anticipated by the present application are all transported across the BBB by receptor mediated processes. Said phrase does therefore not comprise a feature that may distinguish the method from any other method wherein the same peptides are administered into the blood stream.